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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,398	01/31/2001	Christoph Plass	22727/04075	7997

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Pamela A. Docherty
CALFEE, HALTER & GRISWOLD, LLP
1400 McDonald Investment Center
800 Superior Avenue
Cleveland, OH 44114

EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,398	PLASS, CHRISTOPH	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *4-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the amendment filed May 16, 2003. Applicant's amendments and arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. Claims 1-3, 40 and 41 are under consideration. Claims 4-39 are withdrawn from consideration. This action is made final.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS

In particular, the claims have been amended to exclude methods of identifying CpG islands in acute myeloid leukemias and to require the detection of CpG islands in a tumor or neoplasm selected from the group consisting of breast, colon, glioma, head and neck, lung, PNET and testicle tumors or neoplasms.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Konishi (Journal of Oral Pathology and Medicine (1999) 28: 102-106).

Konishi teaches a method for identifying CpG islands which are preferentially methylated in oral squamous cell carcinomas. The reference teaches that RLGS profiling allows for the comparison of methylation patterns in normal versus tumor tissue (page 102). To determine whether DNAs are preferentially methylated in oral squamous cell carcinomas, Konishi uses the method of RLGS. In particular, Konishi (page 103) teaches a method in which

(i) a genomic DNA sample from malignant cells and a genomic DNA sample from contiguous normal squamous epithelium are separately digested with a infrequently cutting, methylation-sensitive restriction enzyme (Not I); (ii) the digested samples are end labeled; (iii) the labeled samples are cut with a second restriction enzyme, EcoRV; (iv) the labeled restriction fragments of step (iii) are separated by gel electrophoresis in 2 separate gels; (v) the restriction fragments are digested with a third restriction enzyme, Hinf I, in the gel; (vi) the fragments are subjected to electrophoresis in a direction perpendicular to the first separation; and (vii) the pattern of restriction fragments from the malignant cells is compared to the pattern of restriction fragments from the non-malignant control cells in order to identify CpG islands that are preferentially methylated in oral squamous cell carcinomas. Konishi (page 102) teaches that it is important to identify the genetic alterations associated with head and neck squamous cell carcinomas and that the method of RLGS allows for the determination of specific genetic abnormalities associated with this disease. Konishi states that cloning and further analysis of the DNA found to be altered in their study will be performed in order to determine the specifics of the alterations (page 106).

3. Claims 1-3 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Smiraglia (reference "AL" cited in the IDS of May 23, 2001).

Smiraglia teaches a method for identifying CpG islands which are preferentially methylated in medulloblastomas, a type of malignant tumor. The reference teaches that RLGS profiling allows for the comparison of methylation patterns in normal versus tumor tissue (page 254). To determine whether DNAs are preferentially methylated in medulloblastomas, Smiraglia uses the method of RLGS. In particular, Smiraglia (pages 255 and 259 and Figure 5) teaches a method in which (i) a genomic DNA sample from primary medulloblastoma and a

genomic DNA sample from normal cells are separately digested with a infrequently cutting, methylation-sensitive restriction enzyme (Not I); (ii) the digested samples are end labeled; (iii) the labeled samples are cut with a second restriction enzyme, EcoRV; (iv) the labeled restriction fragments of step (iii) are separated by gel electrophoresis in 2 separate gels; (v) the restriction fragments are digested with a third restriction enzyme, Hinf I, in the gel; (vi) the fragments are subjected to electrophoresis in a direction perpendicular to the first separation; and (vii) the pattern of restriction fragments from the medulloblastomas is compared to the pattern of restriction fragments from the normal control cells in order to identify CpG islands that are preferentially methylated in medulloblastomas. The reference also teaches cloning and sequencing the DNA preferentially methylated in medulloblastomas.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Konishi in view of Plass (Journal of Oral Pathology and Medicine (1999) 28: 102-106).

Konishi teaches a method for identifying CpG islands which are preferentially methylated in oral squamous cell carcinomas. The reference teaches that RLGS profiling allows for the comparison of methylation patterns in normal versus tumor tissue (page 102 and 105). To determine whether DNAs are preferentially methylated in oral squamous cell carcinomas, Konishi uses the method of RLGS. In particular, Konishi (page 103) teaches a method in which

(i) a genomic DNA sample from malignant cells and a genomic DNA sample from contiguous normal squamous epithelium are separately digested with a infrequently cutting, methylation-sensitive restriction enzyme (Not I); (ii) the digested samples are end labeled; (iii) the labeled samples are cut with a second restriction enzyme, EcoRV; (iv) the labeled restriction fragments of step (iii) are separated by gel electrophoresis in 2 separate gels; (v) the restriction fragments are digested with a third restriction enzyme, Hinf I, in the gel; (vi) the fragments are subjected to electrophoresis in a direction perpendicular to the first separation; and (vii) the pattern of restriction fragments from the malignant cells is compared to the pattern of restriction fragments from the non-malignant control cells in order to identify CpG islands that are preferentially methylated in oral squamous cell carcinomas. Konishi (page 102) teaches that it is important to identify the genetic alterations associated with head and neck squamous cell carcinomas and that the method of RLGS allows for the determination of specific genetic abnormalities associated with this disease. Konishi states that cloning and further analysis of the DNA found to be altered in their study will be performed in order to determine the specifics of the alterations (page 106). However, Konishi does not exemplify determining the sequence of the DNA comprising a CpG island that is methylated in the oral squamous cell carcinoma cells and unmethylated in normal control cells.

However, Plass teaches a method for identifying CpG islands which are preferentially methylated in acute myeloid leukemia, which is a malignant cancer. The reference teaches that RLGS profiling allows for the comparison of methylation patterns in normal versus tumor tissue (page 3159) and states that aberrant methylation in the regulatory regions of expressed genes may play a role in hematologic cancers. Plass also teaches cloning the DNA from normal cells

which corresponds to the DNA that is preferentially methylated in acute myeloid leukemia cells and teaches determining the sequence of at least a portion of this DNA.

In view of the teachings of Plass, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Konishi so as to have obtained a clone from a DNA library which comprises the DNA containing the CpG island that is methylated in the oral squamous cell carcinoma cells and unmethylated in normal control cells and to have sequenced this DNA in order to have further characterized the DNA associated with oral squamous cell carcinoma so as to provided additional information to assist in determining the mechanism of development of this carcinoma.

5. Claims 1-3, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fruhwald (Genes, Chromosomes, & Cancer, (published online 13 September 200, 30: pages 38-47; cited in the IDS of May 14, 2001, reference "AK") in view of Plass.

Fruhwald teaches a method for identifying CpG islands which are preferentially methylated in PNETs. The reference teaches that RLGS profiling allows for the comparison of methylation patterns in normal versus tumor tissue (page 39). To determine whether DNAs are preferentially methylated in supratentorial PNET and medulloblastomas, Fruhwald uses the method of RLGS. Fruhwald (page 42) further teaches cloning the DNA that comprises a CpG island that is methylated in the oral squamous cell carcinoma cells and unmethylated in normal control cells and determining the sequence of this DNA. Fruhwald does not provide the specific details for performing the RLGS profiling.

However, Plass teaches the method of RLGS profiling in which (i) a genomic DNA sample from malignant cells and a genomic DNA sample from non-malignant control cells are

separately digested with a infrequently cutting, methylation-sensitive restriction enzyme (Not I); (ii) the digested samples are end labeled; (iii) the labeled samples are cut with a second restriction enzyme, EcoRV; (iv) the labeled restriction fragments of step (iii) are separated by gel electrophoresis in 2 separate gels; (v) the restriction fragments are digested with a third restriction enzyme, Hinf I, in the gel; (vi) the fragments are subjected to electrophoresis in a direction perpendicular to the first separation; and (vii) the pattern of restriction fragments from the malignant cells is compared to the pattern of restriction fragments from the non-malignant control cells in order to identify CpG islands that are preferentially methylated in malignant acute myeloid leukemia cells (see, for example, page 3164). Plass teaches that the RLGS method is useful to identify novel epigenetic alterations in human cancer that are not detectable by standard methods.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Plass to perform RLGS in the method of Fruhwald in order to have provided an effective means for detecting CpG islands preferentially methylated in PNETs and for identifying DNA sequences associated with the occurrence of PNETs.

6. Claims 1-3, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fruhwald (cited in the IDS of May 14, 2001, reference "AN") in view of Plass.

Fruhwald teaches a method for identifying CpG islands which are preferentially methylated in medulloblastomas. The reference teaches that RLGS profiling allows for the comparison of methylation patterns in normal versus tumor tissue. To determine whether DNAs are preferentially methylated in medulloblastomas, Fruhwald uses the method of RLGS. While Fruhwald teaches that RLGS involves digestion with the methylation sensitive enzyme NotI and

2 dimensional gel electrophoresis (see Figure 1), Fruhwald does not provide the specific details for performing the RLGS profiling. Further, Fruhwald does not teach cloning and sequencing the DNAs preferentially methylated in medulloblastomas.

However, Plass teaches the method of RLGS profiling in which (i) a genomic DNA sample from malignant cells and a genomic DNA sample from non-malignant control cells are separately digested with a infrequently cutting, methylation-sensitive restriction enzyme (Not I); (ii) the digested samples are end labeled; (iii) the labeled samples are cut with a second restriction enzyme, EcoRV; (iv) the labeled restriction fragments of step (iii) are separated by gel electrophoresis in 2 separate gels; (v) the restriction fragments are digested with a third restriction enzyme, Hinf I, in the gel; (vi) the fragments are subjected to electrophoresis in a direction perpendicular to the first separation; and (vii) the pattern of restriction fragments from the malignant cells is compared to the pattern of restriction fragments from the non-malignant control cells in order to identify CpG islands that are preferentially methylated in malignant acute myeloid leukemia cells (see, for example, page 3164). Plass teaches that the RLGS method is useful to identify novel epigenetic alterations in human cancer that are not detectable by standard methods. Plass also teaches cloning and sequencing of the isolated DNAs preferentially methylated in tumor cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Plass to perform RLGS in the method of Fruhwald in order to have provided an effective means for detecting CpG islands preferentially methylated in medulloblastomas and for identifying DNA sequences associated with the occurrence of medulloblastomas. Further, it would have been obvious to one of ordinary skill in the art at the

time the invention was made to have modified the method of Fruhwald so as to have obtained a clone from a DNA library which comprises the DNA containing the CpG island that is methylated in the medulloblastoma and unmethylated in normal control cells and to have sequenced this DNA in order to have further characterized the DNA associated with the occurrence of medulloblastomas so as to provided additional information to assist in determining the mechanism of development of this cancer.

7. Claims 1-3, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Dai (cited in the IDS of May 14, 2001 as reference "AR") in view of Plass.

Dai teaches a method for identifying CpG islands which are preferentially methylated in non-small cell lung carcinomas. The reference teaches that RLGS profiling allows for the comparison of methylation patterns in normal lung tissue versus primary lung tumor tissue. To determine whether DNAs are preferentially methylated in non-small cell lung carcinomas, Dai uses the method of RLGS. Dai further teaches cloning the DNA that comprises a CpG island that is methylated in the non-small cell lung carcinoma cells and unmethylated in normal control cells and determining the sequence of this DNA. Dai does not provide the specific details for performing the RLGS profiling.

However, Plass teaches the method of RLGS profiling in which (i) a genomic DNA sample from malignant cells and a genomic DNA sample from non-malignant control cells are separately digested with a infrequently cutting, methylation-sensitive restriction enzyme (Not I); (ii) the digested samples are end labeled; (iii) the labeled samples are cut with a second restriction enzyme, EcoRV; (iv) the labeled restriction fragments of step (iii) are separated by gel electrophoresis in 2 separate gels; (v) the restriction fragments are digested with a third

restriction enzyme, Hinf I, in the gel; (vi) the fragments are subjected to electrophoresis in a direction perpendicular to the first separation; and (vii) the pattern of restriction fragments from the malignant cells is compared to the pattern of restriction fragments from the non-malignant control cells in order to identify CpG islands that are preferentially methylated in malignant acute myeloid leukemia cells (see, for example, page 3164). Plass teaches that the RLGS method is useful to identify novel epigenetic alterations in human cancer that are not detectable by standard methods.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Plass to perform RLGS in the method of Dai in order to have provided an effective means for detecting CpG islands preferentially methylated in non-small cell lung carcinomas and for identifying DNA sequences associated with the occurrence of non-small cell lung carcinomas in order to provide a better understanding of the mechanisms lung cancer development.

8. Claims 1-3, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Smiraglia (cited in the IDS of May 14, 2001 as reference "AP") in view of Plass.

Smiraglia teaches a method for identifying CpG islands which are preferentially methylated in seninomatous (SE) testicular germ cell tumors, which is a malignant tumor. The reference teaches that RLGS profiling allows for the comparison of methylation patterns in non-malignant cells versus seninomatous testicular germ cell tumors. To determine whether DNAs are preferentially methylated in seninomatous testicular germ cell tumors, Smiraglia uses the method of RLGS. Smiraglia further teaches cloning the DNA that comprises a CpG island that is methylated in the seninomatous testicular germ cell tumors and unmethylated in non-malignant

cells and determining the sequence of this DNA. Smiraglia does not provide the specific details for performing the RLGS profiling.

However, Plass teaches the method of RLGS profiling in which (i) a genomic DNA sample from malignant cells and a genomic DNA sample from non-malignant control cells are separately digested with a infrequently cutting, methylation-sensitive restriction enzyme (Not I); (ii) the digested samples are end labeled; (iii) the labeled samples are cut with a second restriction enzyme, EcoRV; (iv) the labeled restriction fragments of step (iii) are separated by gel electrophoresis in 2 separate gels; (v) the restriction fragments are digested with a third restriction enzyme, Hinf I, in the gel; (vi) the fragments are subjected to electrophoresis in a direction perpendicular to the first separation; and (vii) the pattern of restriction fragments from the malignant cells is compared to the pattern of restriction fragments from the non-malignant control cells in order to identify CpG islands that are preferentially methylated in malignant acute myeloid leukemia cells (see, for example, page 3164). Plass teaches that the RLGS method is useful to identify novel epigenetic alterations in human cancer that are not detectable by standard methods.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Plass to perform RLGS in the method of Smiraglia in order to have provided an effective means for detecting CpG islands preferentially methylated in seninomatous testicular germ cell tumors and for identifying DNA sequences associated with the occurrence of seninomatous testicular germ cell tumors in order to provide a better understanding of the mechanisms of SE development.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

June 23, 2003

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER